Dioxane used as a solvent in the determinations was technical grade which was refluxed over sodium for a minimum of two days and then distilled from sodium as needed. The fraction boiling at 101.5° was used in this work. The benzene for one determination was obtained by distilling thiophene-free benzene from sodium. The fraction boiling at 80–80.5° was taken.

Calculations of the dipole moments from the dielectric constant and refractive index data in Table III were done by the Guggenheim method of initial slopes.[1]

Acknowledgment.—The authors wish to express their gratitude and appreciation for the generous support of this work by the Office of Naval Research.

(19) See reference 10b for further references and discussion.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Internal Condensation of 2,4-Diphenyl-1-butanesulfonyl Chloride to a Five- in Preference to a Seven-membered Cyclic Sulfone[1]

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The preference of five- rather than seven-membered ring sulfone formation by the Friedel–Crafts cyclization of ω-phenylalkanesulfonyl chlorides is demonstrated by the formation of 2,3-dihydro-3-(β-phenylethyl)-benzothiophene-1-dioxide rather than 3-phenylhomothiochroman-1-dioxide from 2,4-diphenyl-1-butanesulfonyl chloride.

Cyclization of ω-phenylalkanesulfonyl chlorides by the Friedel–Crafts method proceeds best when forming the six-membered ring sulfone, while the five- and seven-membered ring compounds are formed in much lower, and approximately equal yields.[2] To determine whether the five- or seven-membered ring sulfone would be formed preferentially when in open competition, 1,5-diphenyl-2-pentanesulfonyl chloride was prepared as outlined.

$$C_6H_5(CH_2)_3MgBr + C_6H_5CH_2CHO \longrightarrow$$

$$C_6H_5(CH_2)_3CH(OH)CH_2C_6H_5 \xrightarrow{PBr_3}$$

$$C_6H_5(CH_2)_3CHBrCH_2C_6H_5 \xrightarrow[2,\ KOH,\ H_2O]{1,\ CS(NH_2)_2}$$

$$C_6H_5(CH_2)_3CH(SH)CH_2C_6H_5 \xrightarrow[AcOH]{Cl_2,\ H_2O}$$

$$C_6H_5(CH_2)_3CH(SO_2Cl)CH_2C_6H_5$$

Unfortunately, the resulting sulfonyl chloride was unstable, losing sulfur dioxide even when stored in a refrigerator; therefore, this approach to the problem was abandoned.

In order to avoid this characteristic instability[3] of secondary sulfonyl chlorides, the primary sulfonyl chloride, 2,4-diphenyl-1-butanesulfonyl chloride, was prepared by the sequence of reactions

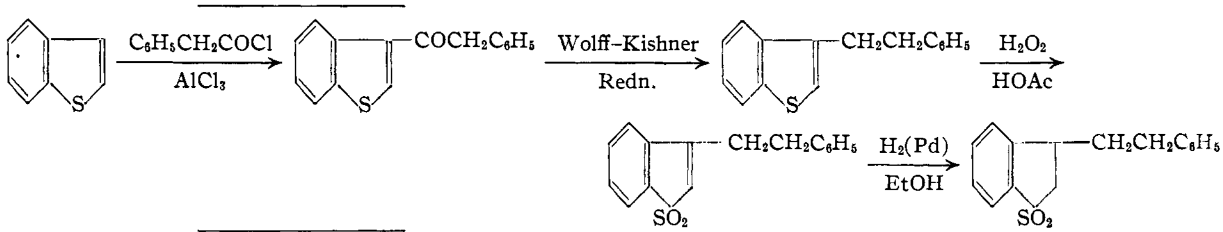
$$C_6H_5CH(CH_2Br)(CH_2)_2C_6H_5 + K_2SO_3 \xrightarrow[140°]{HOCH_2CH_2OH}$$

$$\xrightarrow{PCl_5} C_6H_5CH(CH_2SO_2Cl)(CH_2)_2C_6H_5$$

Cyclization[2] of this sulfonyl chloride yielded 2,3-dihydro-3-(β-phenylethyl)-benzothiophene-1-dioxide; none of the isomeric 3-phenylhomothiochroman-1-dioxide was isolated. This indicates that the five-membered ring sulfone is formed in preference to the seven-membered ring sulfone in the Friedel–Crafts cyclization of phenylalkanesulfonyl chlorides.

2,4-Diphenyl-1-bromobutane was prepared by way of 2,4-diphenylbutyric acid. A new but inferior approach to this acid began by alkylating diethyl phenylmalonate with β-phenylethyl bromide. However, the product, diethyl phenyl-(β-phenylethyl)-malonate, was not saponified by prolonged refluxing with strong alkali; it was hydrolyzed and decarboxylated, with difficulty and in poor conversion, to 2,4-diphenylbutyric acid, using strong sulfuric acid–potassium bisulfate as the reagent.

That the product of the Friedel–Crafts cyclization was 2,3-dihydro-3-(β-phenylethyl)-benzothiophene-1-dioxide and not 3-phenylhomothiochroman-1-dioxide was established by the following independent synthesis of the former compound.



Experimental

1,5-Diphenyl-2-pentanesulfonyl Chloride.—The Grignard reagent[4] of γ-phenylpropyl bromide was treated with phenylacetaldehyde, and the product was distilled at reduced pressure; b.p. 159° (0.7 mm.), $n^{20}D$ 1.5593, yield 57% of theory.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.98; H, 8.41. Found: C, 84.90, 84.95; H, 8.20, 8.09.

This product, 1,5-diphenyl-2-pentanol, was treated with phosphorus tribromide[5] at −5 to 0°. Distillation of the

(1) Taken from Mr. Emrick's and Mr. Miller's M.S. theses.
(2) W. E. Truce and J. P. Milionis, THIS JOURNAL, **74**, 974 (1952).
(3) M. H. Gold and L. J. Druker, *J. Org. Chem.*, **16**, 1510 (1951).
(4) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 306.
(5) *Ibid.*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 358.

bromide was accompanied by the evolution of hydrogen bromide; b.p. 173° (1.8 mm.), $n^{20}D$ 1.5739, yield 71% of theory.

Anal. Calcd. for $C_{17}H_{19}Br$: C, 67.4; H, 6.3. Found: C, 70.68, 70.82; H, 6.57, 6.50.

The bromide was refluxed with thiourea and ethanol.[6,7] The resulting oily isothiouronium bromide was treated with aqueous sodium hydroxide.[6] A heavy oil, with an odor characteristic of mercaptans, was liberated. It could not be crystallized, and distillation at reduced pressure resulted in loss of hydrogen sulfide. The corresponding sulfonyl chloride, obtained by bubbling chlorine through a solution of this product in acetic acid and water at 0°,[6] was also a viscous oil, which decomposed rapidly upon distillation and slowly at 0°.

The sulfonyl chloride was treated with aluminum chloride in nitrobenzene at moderate temperature. The product was a tar from which no crystals could be isolated. Distillation of the tar yielded an extremely small quantity of crystals, which after repeated recrystallization from ethanol and treatment with activated charcoal melted at 173–174° (uncorrected).

Anal. Found: C, 86.10, 85.92; H, 5.66, 5.56.

2,4-Diphenylbutyric Acid.—Sodium (43.5 g., 1.9 g. atoms) dissolved in 425 ml. of absolute ethanol was refluxed 8 hours with 444 g. (1.9 moles) of diethyl phenylmalonate and 344 g. (1.9 moles) of β-phenylethyl bromide. The oil, which separated on pouring the reaction mixture into water, was dried and distilled to give 112 g. (18% yield) of diethyl phenyl-(β-phenylethyl)-malonate, b.p. 235–245° (18 mm.). Refractionation gave a nearly colorless oil, b.p. 232–234° (15 mm.), $n^{20}D$ 1.5324, d^{31} 1.063.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.12; H, 7.12. Found: C, 73.80, 73.93; H, 7.10, 7.02.

Refluxing 97 g. of the above ester with 250 g. of potassium hydroxide in 240 g. of water for 40 hours resulted in a nearly quantitative recovery of the ester. Ninety-six grams of the above ester was dropped slowly into a refluxing mixture of 200 g. of fused potassium acid sulfate, 90 ml. of water and 100 ml. of concd. sulfuric acid. After frothing had nearly stopped, the mixture was refluxed for 5 hours, poured onto ice and the organic layer was extracted with aqueous sodium hydroxide. Acidification of the alkaline layer gave 5.2 g. of product, which after recrystallization had m.p. 74.5–75° (lit.[8] m.p. 75°).

2-Phenyl-3-benzoylpropionic acid[9] was reduced in 84.5% yield by a Wolff–Kishner procedure[10] to 2,4-diphenylbutyric acid.[8] Reduction of the latter compound by lithium aluminum hydride[11] followed by treatment with phosphorus tribromide, gave 1-bromo-2,4-diphenylbutane[12] in 68% over-all yield (based on 2,4-diphenylbutyric acid).

2,4-Diphenyl-1-butanesulfonyl Chloride.—Prolonged refluxing of the above bromide with five times the theoretical amount of saturated aqueous sodium sulfite or potassium sulfite solution resulted in nearly quantitative recovery of unreacted bromide. Furthermore, less than 10% of the bromide reacted after refluxing 57 g. of it for 4.5 hours with a mixture of 101 ml. of water, 125 ml. of ethanol and 50 g. of sodium thiosulfate pentahydrate.

Fifty-two grams (0.18 mole) of 1-bromo-2,4-diphenylbutane, 207 ml. of saturated potassium sulfite solution (1.0 mole) and 420 ml. of ethylene glycol were refluxed 3.5 hours at 126°. One hundred ml. of distillate was removed (two thirds of the original water), permitting the temperature of the reaction mixture to rise to 143°; refluxing was continued for 6 more hours. The material was poured into a mixture of 160 ml. of concd. hydrochloric acid and 440 ml. of water and boiled several minutes to expel sulfur dioxide. Potassium chloride (100 g.) was added, followed by a hot solution of 65 g. of barium chloride in 120 ml. of water. Upon chilling to −5° for 1 hour, the precipitated barium sulfonate was filtered off, washed with 100 ml. of saturated barium chloride and again sucked as dry as possible. The resulting barium sulfonate was converted by metathesis to the corresponding sodium salt. The *p*-toluidine salt melted at 153–154.5°.

Anal. Calcd. for $C_{23}H_{27}O_3NS$: C, 69.49; H, 6.84; N, 3.53. Found: C, 69.43; H, 6.75; N, 3.64.

About 60 g. (*ca.* 0.19 mole) of the powdered, crude sodium 2,4-diphenylbutanesulfonate was intimately mixed with 40 g. (0.19 mole) of phosphorus pentachloride and heated on a steam-bath for 3 hours. The reaction mixture was poured over ice and extracted with 400 ml. of ether. After drying the ether layer over anhydrous calcium chloride, the ether was removed by distillation. The residue was recrystallized from about 425 ml. of petroleum ether (b.p. 90–100°) to yield 13.7 g. (25% yield) of white crystalline 2,4-diphenylbutanesulfonyl chloride, m.p. 69.5–70.0°.

Anal. Calcd. for $C_{16}H_{17}O_2ClS$: C, 62.23; H, 5.55. Found: C, 62.39; H, 5.88.

Its sulfonamide had m.p. 91.0–92.0°.

Anal. Calcd. for $C_{16}H_{19}O_2NS$: C, 66.39; H, 6.62; N, 4.84. Found: C, 65.66; H, 6.76; N, 5.02.

2,3-Dihydro-3-(β-phenylethyl)-benzothiophene-1-dioxide.—2,4-Diphenylbutanesulfonyl chloride (12.7 g.) in 32 g. of nitrobenzene was added slowly to a stirred solution of 6.8 g. of anhydrous aluminum chloride in 64 g. of nitrobenzene at room temperature. The mixture was stirred at room temperature for 1.5 hours and then maintained at 83–90° for 1.5 hours with vigorous stirring. At 70–80° there was observed the evolution of gas (at least 0.41 g. of sulfur dioxide was evolved as determined by conversion to barium sulfate). The reaction mixture was cooled with ice and 50 ml. of concd. hydrochloric acid and 50 g. of ice was added with vigorous stirring. The nitrobenzene layer was washed with 75 ml. of 10% potassium carbonate solution, 50 ml. of 20% hydrochloric acid and finally with 50 ml. of water. The wet nitrobenzene layer was placed in a 500-ml. Claisen flask and 70 ml. of nitrobenzene was distilled under 15–17 mm. pressure. The remaining material was steam distilled until virtually no more oil smelling of nitrobenzene steam distilled over (about 750 ml. of steam distillate being collected to this point). The flask was cooled to 5° and the water was decanted from the black plastic material left in the flask. The black residue was refluxed for 15 minutes with 150 ml. of absolute alcohol and 5.0 g. of decolorizing carbon, which absorbed 5.5 g. of brown-black tar. The alcoholic filtrate gave 4.7 g. (42%) of thick yellow oil, which slowly crystallized, m.p. 71–75°. After one recrystallization from 80% alcohol, the material weighed 3.6 g. (32%; this yield compares favorably with previously reported work[2]) and had m.p. 77.5–78.5°; m.p. 81.5–82° after two more recrystallizations. This material produced no depression in m.p. of an authentic sample of 2,3-dihydro-3-(β-phenylethyl)-benzothiophene-1-dioxide (see below), and microscopic examination showed the crystals of the two samples to be the same in shape and size.

In an effort to isolate the seven-membered cyclic sulfone, the tars and mother liquors resulting from the preceding operations were combined and evaporated to dryness. The residue, dissolved in a benzene–petroleum ether mixture, was chromatographed on alumina. Upon stripping various sections of the extruded column with hot chloroform, the only products isolated were black tar (av. mol. wt. > 415 by camphor method) and 2,3-dihydro-3-(β-phenylethyl)-benzothiophene-1-dioxide.

Twelve grams of 3-phenylacetylbenzothiophene,[13] 67 ml. of diethylene glycol and 17 ml. of 64% hydrazine hydrate were refluxed for 2.5 hours. Six grams of potassium hydroxide was added and the reaction mixture was distilled until the reaction temperature reached 145°, after which the mixture was refluxed for 2 hours. More distillate was removed until the reaction temperature rose to 195°, after which refluxing was resumed for 2.5 hours more. The cooled mixture was then poured into 130 ml. of water and 50 ml. of ether. The ether layer was washed with 30 ml. of water, and after drying the ether was evaporated to yield 9.9 g. (87%) of a thick yellow oil. The oil was fractionally distilled; the middle fraction was a pale yellow oil, b.p. 215–219° (15 mm.), which formed low-melting white crystals on standing at room temperature, m.p. 89–90°, after recrystallization.

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(8) E. P. Kohler and R. H. Kimball, THIS JOURNAL, **55**, 4637 (1933).

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(10) "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 391.

(11) *Ibid.*, Vol. VI, 1951, p. 491.

(12) J. D. Rose and R. A. Gale, *J. Chem. Soc.*, 795 (1949).

(13) N. P. Buu-Hoi and P. Cagniant, *Rec. trav. chim.*, **67**, 64 (1948).

Anal. Calcd. for $C_{16}H_{14}S$: C, 80.64; H, 5.92. Found: C, 81.00; H, 6.15.

Seven grams of 3-(β-phenylethyl)-benzothiophene, 20 ml. of acetic anhydride, 30 ml. of glacial acetic acid and 35 ml. of 30% hydrogen peroxide[14] were refluxed for 1.5 hours. At the end of the reflux time, 150 ml. of ice-water was added, followed by 40 g. of sodium hydroxide. The mixture was extracted with 300 ml. of benzene. After evaporating the benzene on a steam-cone, and allowing to stand at room temperature for 24 hours, white crystals were formed. After recrystallizing the product twice from 95% ethanol, 2.9 g. (36%) of 3-(β-phenylethyl)-benzothiophene-1-dioxide was obtained; m.p. 89.5–90.5°.

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.09; H, 5.22. Found: C, 70.99; H, 5.41.

(14) F. G. Bordwell, *et al.*, THIS JOURNAL, **71**, 1704 (1949).

To a solution of 2.0 g. of 3-(β-phenylethyl)-benzothiophene-1-dioxide in 100 ml. of absolute ethanol, 0.08 g. of 5% palladium on animal charcoal was added, and the material was hydrogenated[15] under an initial pressure of 45.6 p.s.i. The hydrogenation was continued for 1 hour even though no more hydrogen was taken up after the first 20 minutes. After filtering and evaporating to 25 ml. on a steam-cone and chilling in an ice–salt-bath, a nearly colorless, pasty oil was initially deposited followed later by white crystals. The crystals (1.2 g.) melted at 75–77° and after two recrystallizations from ethanol melted at 78.5–80.0°.

Anal. Calcd. for $C_{16}H_{16}O_2S$: C, 70.54; H, 5.92. Found: C, 70.37; H, 5.88.

(15) F. G. Bordwell, *et al.*, *ibid.*, **72**, 1985 (1950).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND THE NATIONAL INSTITUTES OF HEALTH]

Studies on Carboline Anhydronium Bases

BY BERNHARD WITKOP[1]

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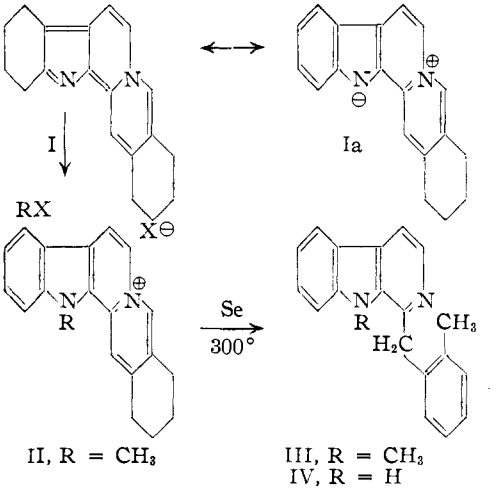
Methylsempervirine chloride (II), the quaternary salt from the markedly hypotensive alkaloid sempervirine (I ⇄ Ia) on treatment with selenium yields N-methylyobyrine (III) and yobyrine (IV). On refluxing with sodium borohydride in methanol II furnishes methylhexahydrosempervirine in which the position of the double bond may be at $\Delta_{14,15}$ (in analogy to the formation of arecoline from methyl nicotinate) or possibly at $\Delta_{15,20}$ (IX) or $\Delta_{20,21}$ (X). N-Methylyohimbane (VIII), an isomer of methyloctahydrosempervirine (VII) was prepared by the methylation of yohimbane; on catalytic oxidation with platinum catalyst in glacial acetic acid it formed the cation (XIII) of methyltetradehydroyohimbane. The latter dehydrogenation at room temperature is considered the model reaction for the dehydrogenation of tetrahydroharmans in the plant leading to sempervirine, serpentine, alstonine and other anhydronium bases. Spectrophotometric and pharmacological data together with some observations in the 2-carboline series are presented.

Robinson has suggested the name *anhydronium bases* for the colored anhydro derivatives of aromatic onium hydroxides of which he prepared representatives in the 3-,[2] 4- and 2-carboline,[3] quindoline, indophenazine and other series.[3] Within the last few years, the alkaloids sempervirine[4,5] serpentine,[6] alstonine[6,7] and cryptolepine,[8] have been recognized as naturally occurring anhydronium bases of the 3-carboline and quindoline type. Recent reports on the beneficial effect of serpentine hydrochloride on patients suffering from hypertension[9] has again directed attention to natural and synthetic anhydronium bases, especially in the yohimbine series, and some recent studies on dehydrogenation and hydrogenation in this series, together with related observations made several years ago, are reported in this paper.

Sempervirine, isolated from the American yellow jasmine[10] and later from *Mostuea Buchholzii*[11] was recognized as the first naturally occurring anhydronium base (I ⟷ Ia) by R. B. Woodward[4] who predicted correctly the absence of an NH-imino band[12] in the infrared spectrum of sempervirine (Fig. 1a). The unusually high dipole moment of I (7–8 *D*[5,13] in benzene or dioxane) offers good evidence for the actual existence of Ia which adds alkyl halides[4,5] in the reverse fashion in which tertiary bases in this series normally react. The proof for the position of the methyl group in methylsempervirine chloride (II) was (besides the latter



(1) National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland.

(2) With regard to nomenclature, *cf.* J. M. Gulland, R. Robinson, J. Scott and S. Thornley, *J. Chem. Soc.*, 2926 (1929).

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(10) For a review, *cf.* L. Marion, "The Indole Alkaloids," in "The Alkaloids," edited by R. H. F. Manske and H. L. Holmes, Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 432.

(11) E. Gellert and H. Schwarz, *Helv. Chim. Acta*, **34**, 779 (1951).

(12) *Cf.* O. E. Edwards and L. Marion, THIS JOURNAL, **71**, 1695 (1949).[8]

(13) K. A. Jensen, *Acta Chem. Scand.*, **3**, 1447 (1949).